TREATMENT CUSHING'S SYNDROME

Overt Cushing's is associated with a poor prognosis if left untreated. In ACTH-independent disease, treatment consists of surgical removal of the adrenal tumor. For smaller tumors, a minimally invasive approach can be used, whereas for larger tumors and those suspected of malignancy, an open approach is preferred.

In Cushing's disease, the treatment of choice is selective removal of the pituitary corticotrope tumor, usually via an endoscopic transsphenoidal approach. This results in an initial cure rate of 70–80% when performed by a highly experienced surgeon. However, even after initial remission following surgery, long-term follow-up is important because late relapse occurs in a significant number of patients. If pituitary disease recurs, there are several options, including second surgery, radiotherapy, stereotactic radiosurgery, and bilateral adrenalectomy. These options need to be applied in a highly individualized fashion.

In some patients with very severe, overt Cushing's (e.g., difficult to control hypokalemic hypertension or acute psychosis), it may be necessary to introduce medical therapy to rapidly control the cortisol excess during the period leading up to surgery. Similarly, patients with metastasized, glucocorticoid-producing carcinomas may require long-term antiglucocorticoid drug treatment. In case of ectopic ACTH syndrome, in which the tumor cannot be located, one must carefully weigh whether drug treatment or bilateral adrenalectomy is the most appropriate choice, with the latter facilitating immediate cure but requiring life-long corticosteroid replacement. In this instance, it is paramount to ensure regular imaging follow-up for identification of the ectopic ACTH source.

Oral agents with established efficacy in Cushing's syndrome are metyrapone and ketoconazole. Metyrapone inhibits cortisol synthesis at the level of 11β-hydroxylase (Fig. 406-1), whereas the antimycotic drug ketoconazole inhibits the early steps of steroidogenesis. Typical starting doses are 500 mg tid for metyrapone (maximum dose, 6 g) and 200 mg tid for ketoconazole (maximum dose, 1200 mg). Mitotane, a derivative of the insecticide o,p'DDD, is an adrenolytic agent that is also effective for reducing cortisol. Because of its side effect profile, it is most commonly used in the context of adrenocortical carcinoma, but low-dose treatment (500–1000 mg/d) has also been used in benign Cushing's. In severe cases of cortisol excess, etomidate can be used to lower cortisol. It is administered by continuous IV infusion in low, nonanesthetic doses.

After the successful removal of an ACTH- or cortisol-producing tumor, the HPA axis will remain suppressed. Thus, hydrocortisone replacement needs to be initiated at the time of surgery and slowly tapered following recovery, to allow physiologic adaptation to normal cortisol levels. Depending on degree and duration of cortisol excess, the HPA axis may require many months or even years to resume normal function.

MINERALOCORTICOID EXCESS

Epidemiology Following the first description of a patient with an aldosterone-producing adrenal adenoma (*Conn's syndrome*), mineralocorticoid excess was thought to represent a rare cause of hypertension. However, in studies systematically screening all patients with hypertension, a much higher prevalence is now recognized, ranging from 5 to 12%. The prevalence is higher when patients are preselected for hypokalemic hypertension.

Etiology The most common cause of mineralocorticoid excess is primary aldosteronism, reflecting excess production of aldosterone by the adrenal zona glomerulosa. Bilateral micronodular hyperplasia is somewhat more common than unilateral adrenal adenomas (Table 406-3). Somatic mutations in channels and enzymes responsible for increasing sodium and calcium influx in adrenal zona glomerulosa cells have been identified as prevalent causes of aldosterone-producing adrenal adenomas (Table 406-3) and, in the case of germline mutations, also of primary aldosteronism due to bilateral macronodular adrenal hyperplasia. However, bilateral adrenal hyperplasia as a cause of mineralocorticoid excess is usually micronodular but can also contain larger nodules that might be mistaken for a unilateral adenoma. In rare instances, primary aldosteronism is caused by an adrenocortical carcinoma. Carcinomas should be considered in younger patients and in those with larger tumors, because benign aldosterone-producing adenomas usually measure <2 cm in diameter.

A rare cause of aldosterone excess is glucocorticoid-remediable aldosteronism (GRA), which is caused by a chimeric gene resulting

TABLE 406-3 CAUSES OF MINERALOCORTICOID EXCESS

Causes of Mineralocorticoid Excess	Mechanism	%
Primary Aldosteronism		
Adrenal (Conn's) adenoma	Autonomous aldosterone excess can be caused by somatic (intratumor) mutations in the potassium channel GIRK4 (encoded by *KCNJ5*; identified as cause of disease in 40% of aldosterone-producing adenomas; rare germline mutations can cause bilateral macronodular adrenal hyperplasia). Further causes include somatic mutations affecting the α-subunit of the Na^+/K^+-ATPase (encoded by *ATP1A1*), the plasma membrane calcium-transporting ATPase 3 (encoded by *ATP2B3*), and somatic or germline mutations in *CACNA1D* encoding the voltage-gated calcium channel Cav1.3. All mutations result in upregulation of CYP11B2 and hence aldosterone synthesis.	60
Bilateral (micronodular) adrenal hyperplasia	Autonomous aldosterone excess	60
Glucocorticoid-remediable hyperaldosteronism (dexamethasone-suppressible hyperaldosteronism)	Crossover between the *CYP11B1* and *CYP11B2* genes results in ACTH-driven aldosterone production	<1
Other Causes (Rare)		<1
Syndrome of apparent mineralocorticoid excess (SAME)	Mutations in *HSD11B2* result in lack of renal inactivation of cortisol to cortisone, leading to excess activation of the MR by cortisol	
Cushing's syndrome	Cortisol excess overcomes the capacity of HSD11B2 to inactivate cortisol to cortisone, consequently flooding the MR	
Glucocorticoid resistance	Upregulation of cortisol production due to GR mutations results in flooding of the MR by cortisol	
Adrenocortical carcinoma	Autonomous aldosterone and/or DOC excess	
Congenital adrenal hyperplasia	Accumulation of DOC due to mutations in *CYP11B1* or *CYP17A1*	
Progesterone-induced hypertension	Progesterone acts as an abnormal ligand due to mutations in the MR gene	
Liddle's syndrome	Mutant ENaC β or γ subunits resulting in reduced degradation of ENaC keeping the membrane channel in open conformation for longer, enhancing mineralocorticoid action	

Abbreviations: ACTH, adrenocorticotropic hormone; DOC, deoxycorticosterone; ENaC, epithelial sodium channel; GR, glucocorticoid receptor; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; MR, mineralocorticoid receptor.